

Bendtsen L, Jensen R, Olesen J. A non-selective (amitriptyline), but non a selective (citalopram), serotonin reuptake inhibitor is effective in the prophylactic treatment of chronic tension-type headache. J Neurol Neurosurg Psychiatry 1996;61:285-290.

Design: Randomized crossover trial

Population/sample size/setting:

- 40 patients (25 women, 15 men, mean age 40) treated for chronic tension headache at a university neurology department in Denmark
- Inclusion criteria were age 18 to 65 with a diagnosis of chronic tension type headache according to International Headache Society criteria
- Exclusion criteria were previous participation in a clinical trial, migraine more than one day per month, serious somatic or psychiatric diseases, misuse of simple analgesics (more than 2 g of aspirin per day), regular intake of opiates or benzodiazepines, and previous treatment with antidepressants

Main outcome measures:

- All patients had a four week run-in period, during which they completed a headache diary; this diary was maintained throughout the study
 - o Diary recorded intensity and duration of headaches, analgesic use, side effects of medication, aggravating factors, nausea, photophobia and phonophobia
- Three medications were given in an order determined by randomization: placebo, amitriptyline, and citalopram; randomization was done in blocks of six to accommodate each of the six permutations of treatment order
- Each of the three drugs was given for eight weeks, and the treatment periods were separated by washout periods of two weeks
- The drugs were designed to make them identical in appearance and taste, and prepared so that two tablets were taken each day 2-3 hours before bedtime
- Placebo was taken during the washout periods
- Amitriptyline dose was titrated from a starting dose of 25 mg to a final dose of 75 mg; citalopram dose was 20 mg
- The main outcome was derived from the headache diaries, and was calculated as the area under the curve (AUC) of the headache entries; this was defined as the intensity (scale of 0 to 10) times the duration of each headache
 - o The AUC was the sum of daily headache intensity x duration for the last 4 weeks of each 8-week treatment period
- Follow-up visits were done every four weeks, when medication compliance was ascertained and new medication was issued
- Separate tests were done to detect carryover effects and period effects
- Six patients withdrew from the study before completion: one due to amitriptyline side effects, one due to pregnancy, two due to lack of effect of placebo, and two due to lack of effect of citalopram
- In the 34 who completed the study, there was a significant effect of amitriptyline; the AUC was reduced by 30% compared to placebo

- The AUC was not significantly reduced by citalopram; the reduction was only 12% compared to placebo
- Most of the AUC reduction was due to decreased duration of headache rather than headache intensity
- Analgesic use was a secondary outcome, and was also reduced by amitriptyline (from 41 doses/4 weeks during the run-in to 25 doses/4 weeks during amitriptyline)
- There were no significant carryover or period effects
- Amitriptyline had more side effects (drowsiness and dry mouth) than placebo or citalopram

Authors' conclusions:

- Amitriptyline has a highly significant effect in the treatment of chronic tension-type headaches
- The patient population had tried numerous interventions for their headaches, and represent a treatment-resistant group of headache patients
- Because of mild side-effects at the fairly low doses of amitriptyline used in the study, it is reasonable to consider every patient with chronic tension-type headaches for a trial of amitriptyline
- The study with its crossover design had sufficient power to detect a therapeutic effect of citalopram, and a clinically important effect is unlikely

Comments:

- The study utilizes the efficiencies of the crossover trial effectively: the administration of the three drugs, the washout periods, and the measurement of treatment effect are all done with a minimum of bias
- The study also had separate tests for period and carryover effects, which many crossover trials fail to accomplish

Assessment : High quality for evidence that amitriptyline has favorable therapeutic effects for chronic tension-type headaches